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EXAMINER	
LEE, JAE W	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/538,823	HUBER ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/17/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-11 and 22-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-11 and 22-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/11/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

Claims 1-5, 8-11 and 22-33 are pending in this application.

In response to the previous Office action, a non-Final rejection (mailed on 09/19/2007), Applicants filed a response and amendment received on 03/17/2008. Said amendment canceled Claims 6, 7 and 12-21, amended Claims 1, 3-5, 8, 9 and 11, and added Claims 22-33. Thus, Claims 1-5, 8-11 and 22-33 are at issue and present for examination.

Applicants' arguments filed on 03/17/2008, have been fully considered, and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restrictions

Newly amended claims 1, 9, 11, 24, 29 and 32 (all other claims dependent therefrom) are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: SIRT4, SIRT5, SIRT6 and SIRT7 were not claimed originally (see claims filed on 06/13/2005). As such, they have never been

considered in the Restriction/Election requirement (see office action mailed on 10/04/2006), and examined on the merits.

It is noted by the Examiner that the generic claim 1 is no longer the same generic claim compared to its original presentation but rather a Markush-type generic claim. According to MPEP 803.02, while it is improper for the Office to refuse to examine that which applicants regard as their invention, if the subject matter in a Markush-type claim lacks unity of invention, the Office is not required to examine all of the members of Markush group. According to MPEP 803.02, the unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature essential to that utility. In the instant case, while all the members of the Markush group are SIRT proteins having deacetylase activity, there is no disclosed structural feature essential to the activity as recited and they do not appear to share a substantial structural feature as evidenced by Frye et al. (Biochemical and Biophysical Research Communications 260:273-279, 1999; cited in the specification) in Figure 2, where the sequence alignment of SIRT1, SIRT2, SIRT3, SIRT4 and SIRT5 is shown. Furthermore, each of the SIRT proteins recited has a different amino acid sequence, and they are not substantially related structurally as antibodies which will detect one will not detect the others. In addition, each SIRT protein will not render the other SIRT proteins recited in the Markush group as obvious variants. Therefore, the previous of election of species is withdrawn and a new restriction requirement is being made. A supplemental restriction requirement is required in view of the plurality of patentable distinct inventions claimed, and it is deemed proper because the

supplemental restriction is at the discretion of the Examiner as set forth in MPEP 802 and 37 CFR 1.142.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 1-5, 8-11 and 22-33, drawn to a method of evaluating a compound, the method comprising contacting a SIR polypeptide having deacetylase activity with a compound, in the presence of a cytochrome c polypeptide, wherein said SIR polypeptide is SIRT1 as set forth in SEQ ID NO: 1.

Group II, claims 1-5, 8-11 and 22-33, drawn to a method of evaluating a compound, the method comprising contacting a SIR polypeptide having deacetylase activity with a compound, in the presence of a cytochrome c polypeptide, wherein said SIR polypeptide is SIRT2 as set forth in SEQ ID NO: 2.

Group III, claims 1-5, 8-11 and 22-33, drawn to a method of evaluating a compound, the method comprising contacting a SIR polypeptide having deacetylase activity with a compound, in the presence of a cytochrome c polypeptide, wherein said SIR polypeptide is SIRT3 as set forth in SEQ ID NO: 3.

Group IV, claims 1-5, 8-11 and 22-33, drawn to a method of evaluating a compound, the method comprising contacting a SIR polypeptide having deacetylase activity with a compound, in the presence of a cytochrome c polypeptide, wherein said SIR polypeptide is SIRT4 as set forth in SEQ ID NO: 4.

Group V, claims 1-5, 8-11 and 22-33, drawn to a method of evaluating a compound, the method comprising contacting a SIR polypeptide having deacetylase activity with a compound, in the presence of a cytochrome c polypeptide, wherein said SIR polypeptide is SIRT5 as set forth in SEQ ID NO: 5.

Group VI, claims 1-5, 8-11 and 22-33, drawn to a method of evaluating a compound, the method comprising contacting a SIR polypeptide having deacetylase activity with a compound, in the presence of a cytochrome c polypeptide, wherein said SIR polypeptide is SIRT6 as set forth in SEQ ID NO: 6.

Group VII, claims 1-5, 8-11 and 22-33, drawn to a method of evaluating a compound, the method comprising contacting a SIR polypeptide having deacetylase activity with a

compound, in the presence of a cytochrome c polypeptide, wherein said SIR polypeptide is SIRT7 as set forth in SEQ ID NO: 7.

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. The technical feature that is shared among the Applicants' Groups of inventions is drawn to methods for evaluating a compound for its ability to modulate SIRT 1-7 proteins' deacetylase activity in the presence of cytochrome c polypeptide. However, Frye teaches human SIRT1-5, and many other related SIR polypeptides, and demonstrates how different their structures are (see Figure 3 on pg. 277, R.A. Frye, Biochemical and Biophysical Research Communications 260, 273–279 (1999), See attached reference). Therefore, the shared technical feature of the Groups is not a "special technical feature", and unity of invention between the Groups does not exist.

It is noted by the Examiner that in view of applicant's previous election of species SIRT1, which is analogous to Group I in the instant supplemental restriction, and the fact that applicant has already received an office action on the merits on the elected invention, the previous election of species will be considered a response to the new supplemental restriction requirement being made. Accordingly, SIRT2 (SEQ ID NO: 2),

SIRT3 (SEQ ID NO: 3), SIRT4 (SEQ ID NO: 4), SIRT5 (SEQ ID NO: 5), SIRT6 (SEQ ID NO: 6), and SIRT7 (SEQ ID NO: 7) are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Objections to the Specification

The previous objection for not complying with the sequence rules as set forth in 37 CFR 1.821(a)(1) and (a)(2), is withdrawn because Applicants have deleted the recitation of "SEQ ID NO: 16."

Claim Objections

The previous objection of Claim 4 for reciting "the cytochrome c polypeptide is human," is withdrawn because Applicants have replaced the noted phrase to "human cytochrome c polypeptide."

The previous objection of Claims 6-8 for not writing out the abbreviations, i.e., "SIR" or "SIRT," is withdrawn because Applicants have inserted the phrase, "Silent Information Regulator (SIR)" in claim 1.

Claims 1, 8, 9, 11, 24, 29 and 32 remain objected to for containing non-elected subject matter, i.e., SIRT2 (SEQ ID NO: 2) and SIRT3 (SEQ ID NO: 3). Although Applicants have pointed out in the previous restriction requirement discloses that SIRT 2 and SIRT3 were part of a species election, claimed methods as they relate to the

remaining SIR proteins other than the elected SIRT1, i.e., SIRT2-SIRT7, will not be rejoined as they are no longer considered rejoinable species for the reasons stated above in the supplemental restriction.

Claims 1, 9, 11, 24, 29, and 32 are objected to for the recitation of "SIR protein," which can be improved with respect to consistency. The Examiner suggests replacing the noted phrase with ---SIR polypeptide---.

Claims 24, 29 and 32 are objected to for the recitation of "a nucleic acid," which can be improved with respect to form. The Examiner suggests replacing the noted phrase with ---polynucleotide--- since a single nucleic acid molecule cannot encode an amino acid sequence.

Claim 3 is objected to for reciting "cytochrome c polypeptide is full length cytochrome c polypeptide," which can be improved with respect to grammar. The Examiner suggests inserting "a" in front of "full length".

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 8-11 and 22-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 8, 9, 11, 22-25, 29 and 32 (all other claims dependent therefrom) recite the phrase, "SIRT1 (SEQ ID NO: 1)" which is unclear and indefinite. According to the specification on page 19, lines 26-28, "[t]he term "SIRT1 proteins" or "SIRT1 polypeptides" refers to a polypeptide that is *at least 25% identical to the 250 amino acid conserved SIRT1 catalytic domain, amino acid residues 258 to 451 of SEQ ID NO:2*" (italicized for added emphasis). As such, it is unclear and indefinite as to whether or not SIRT1 is being limited to SEQ ID NO: 1 inside the parenthesis or as defined in the specification on page 19 as described above. In the interest of advancing prosecution, the SIRT1 is interpreted to be limited to SEQ ID NO: 1. The Examiner suggests replacing the noted phrase with ---SEQ ID NO: 1--- to clarify this issue. If Applicants do not agree with the Examiner's interpretation of the noted phrase, and if the claims are not amended as suggested by the Examiner, it is indicated that 112 1st paragraph rejections may be re-introduced for the reasons of record and this will not be considered a new grounds of rejection.

Claims 24-26, 29, 30, 32 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24, 25, 29 and 32 (26, 30 and 33 dependent therefrom) recite the phrase "high stringency conditions (hybridizes in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C)" which is unclear and indefinite. The reason is that absent a statement of the conditions under which the hybridization reaction is performed, polynucleotides which will hybridize under some hybridization conditions will not necessarily hybridize under different conditions. Although a condition is recited inside the parenthesis, it is unclear whether or not the phrase inside the parenthesis should be considered as a part of claim limitations or a mere example of many conditions that can be used for the hybridization reaction. In addition, Applicants state that "[s]pecific hybridization conditions referred to herein are as follows: ... 3) high stringency hybridization conditions in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C" on page 24, line 29 continuing to page 25. However, this fails to define what is encompassed by "high stringency conditions" because of the preceding sentences on page 24, lines 24-29,

> "As used herein, the term "hybridizes under low stringency, medium stringency, high stringency, or very high stringency conditions" describes conditions for hybridization and washing. *Guidance for performing hybridization reactions can be found in Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6, which is incorporated by reference. Aqueous and nonaqueous methods are described in that reference and either can be used*" (italicized for added emphasis).

While pages 24-25 of the specification describes some conditions which are intended to be highly stringent, there is nothing to suggest that other conditions would not also be included within the scope of this phrase and in the art what is considered highly stringent varies widely depending on the individual situation as well as the person making the determination. As a consequence, it is unclear how homologous to the complement sequence of a gene encoding SEQ ID NO: 1, a sequence must be to be included within the scope of these claims. In the interest of advancing prosecution, the phrase within the parenthesis is interpreted to be a part of claim limitations. The Examiner suggests that Applicants delete the parenthesis so that the noted phrase is clearly a part of the claim language.

Claims 1-5, 8-11 and 22-33 recite the phrase "a cytochrome c polypeptide," which is unclear and indefinite. While one of skill in the art would conclude that the term refers to a polypeptide which has all the functional characteristics associated with a cytochrome C, claims 4 and 5 suggest that the term also encompasses any fragment, even those having 3 amino acid residues, of a protein having cytochrome C activity. This is unclear and confusing because not all fragments of a protein will have the cytochrome C activity. Since the claims appear to encompass contacting the SIR protein with a test compound in the presence of any fragment of cytochrome c including those that comprise at least 2 amino acid residues, it is unclear as to how one could obtain deacetylation of any fragment of cytochrome c comprising at least two amino acid residues.

Claims 11 and 32 are indefinite in the recitation of the step, "contacting a cell which expresses the SIR polypeptide and a cytochrome c polypeptide with the test compound," because the steps prior to the noted step already require contacting the SIR polypeptide and evaluating whether there is a modulation. Essentially, the noted step is repeating the same steps prior to the noted phrase. It is noted by the Examiner that the noted step will not be given a patentable weight, and as such, the Examiner will interpret the claimed methods as not comprising the noted step.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The previous rejection of Claims 1-11 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicants amendment based on the Examiner's interpretation as described above in 112 2nd paragraph rejection (see supra).

Claims 24-26, 29, 30, 32 and 33 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to a genus of methods of evaluating a compound, the method comprising [1] contacting a Silent Information Regulator (SIR) polypeptide having deacetylase activity, or [2] contacting a cell which expresses a SIR polypeptide having deacetylase activity, with a compound, in the presence of a cytochrome c polypeptide, wherein the SIR polypeptide comprises an amino acid sequence that is encoded by a nucleic acid that hybridizes under high stringency conditions (hybridizes in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C) to the complement of a nucleic acid encoding an amino acid sequence of a SIR protein selected from the group consisting of: SIRT1 (SEQ ID NO: 1); SIRT2 (SEQ ID NO: 2); and SIRT3 (SEQ ID NO: 3).

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of [compositions or methods], it must be clear that: (1) the identifying characteristics of the claimed [compositions or methods] have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The specification discloses only a single representative species of a genus of polypeptides, human SIRT1, i.e., SEQ ID NO: 1, which can be used by the claimed method. However, this single disclosed species fails to provide adequate written

description for methods of using a genus of nucleic acids that hybridizes under 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C to the complement of a nucleic acid encoding an amino acid sequence of SEQ ID NO: 1. The reason is two fold. The term "complement of a nucleic acid" does not limit the size of the complement, thus a complement of a nucleic acid can be a nucleic acid of any size which is complementary to the reference polynucleotide. For example, an oligonucleotide having two nucleic acids which are complementary to a reference polynucleotide are considered "complements". Therefore, the recited genus of proteins encompasses proteins having deacetylase activity encoded by nucleic acids which hybridize to a small fragment of a polynucleotide encoding the protein of SEQ ID NO: 1. Furthermore, under the conditions recited, even if it is assumed that the term "the complement" reads as "the full length complement", the claims still require a genus of proteins having at least 58% sequence identity to the polypeptide of SEQ ID NO: 1. . A calculation of the Tm of the polynucleotide recited in claims 24-26, 29, 30, 32 and 33 shows that under the hybridization conditions recited, the polynucleotides that can be used in the claimed methods can be approximately 86% sequence identical to the polynucleotides that encode SEQ ID NO: 1 (2241 nucleotides = 3x747; SEQ ID NO: 1=747 amino acids). Using the well known equation of Meinkoth and Wahl (Current Protocols in Molecular Biology, Hybridization Analysis of DNA Blots, pages 2.10.8-2.10.11, 1993, see attached), Tm = 81.5 °C +16.6x$\log_{10}$[Na+] +0.41x(%GC) - .61x(%form) – 500/L, the corresponding Tm for the polynucleotide recited is approximately 79 °C assuming a G+C content of 50% and neglecting the term 500/L since L (length of polynucleotide) is ~2241 nucleotides (79 °C = 81.5 + 16.6x$\log_{10}$[3.9/100] +0.41x(%50) - .61(%form = 0); for 20xSSC the molar concentration of Na+ is

3.9). As known in the art, Tm is reduced by approximately 1 °C for each 1% mismatching, therefore under the conditions recited (0.2xSSC and 65 °C), a wash at 65 °C is equivalent to approximately 14% mismatching (14% = 79°C – 65°C). This level of mismatching amounts to 313-314 nucleotides which can be modified (313.74 = 0.14x2241) within the polynucleotides that encode SEQ ID NO: 1. If one assumes that all these mismatches results in codon changes, such polynucleotide would encode a protein having at least 58% sequence identity to SEQ ID NO: 1 (58% = 100 – 314x100/747; SEQ ID NO: 1 = 747 amino acids).

As such, one of skill in the art would not have recognized that Applicants were in possession of the genus of proteins that can be used in the claimed methods, i.e., any polypeptide having 58% sequence identity to SEQ ID NO: 1, while having the deacetylase activity, because the specification does not provide adequate description of the genus of nucleic acids encoding the required proteins by identifying structural features associated with the recited activity, and/or how such structural features correlate to the function recited, i.e., the deacetylase activity.

Given the lack of additional representative species of the above-mentioned genera, as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the recently revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

It is noted by the Examiner that this rejection is necessitated by Applicants' amendment.

Claims 1-5, 8-10, and 22-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for an *in vitro* method of measuring deacetylation activity of human SIRT1 comprising the amino acid sequence as set forth in SEQ ID NO: 1, on chemically acetylated polypeptides having cytochrome C activity, and a method of contacting human SIRT1 comprising the amino acid sequence as set forth in SEQ ID NO: 1 with a protein having cytochrome c activity, wherein said human SIRT1 is expressed in *isolated cells* in the presence of a test compound (italicized for added emphasis), does not reasonably provide enablement for [1] any *in vivo* or *in vitro* method of evaluating a compound, the method comprising contacting a Silent Information Regulator (SIR) polypeptide having deacetylase activity, wherein said polypeptide is encoded by a nucleic acid that hybridizes under the recited conditions to the full length complement or a fragment of a nucleic acid encoding the polypeptide of SEQ ID NO: 1, wherein the SIR polypeptide having deacetylase activity is contacted with any fragment of a protein having cytochrome C activity, or [2] a method of evaluating a compound, the method comprising contacting a non-isolated cell which expresses the polypeptide of SEQ ID NO: 1 with a protein having cytochrome C activity in the presence of a test compound, The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 1-11. In response to this rejection, Applicants have amended claims 1, 3, 5, 8, 9 and 11, cancelled claims 6-7 and added claims 22-33, and traverse the rejection as it applies to the newly amended claims.

Applicants argue that the specification disclose the use of transgenic organisms on page 38, lines 9-12, and how to perform assays in model organism on page 53, line 7 to page 57, line 2. Applicants point out examples of cells that can be used and examples of how to use the cells are provided, e.g., at page 3, lines 4-8; page 4, line 15 to page 5, line 5; page 6, lines 8-29; page 7, line 10 to page 8, line 21; page 9, lines 1-7; page 10 line 23 to page 13, line 26; page 17, lines 3-8.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of claimed methods encompasses the use of any cell within transgenic organism as well as practicing the claimed method in vivo. However, the specification fails to disclose a single transgenic organism that can be used to screen compounds that modulate the interaction between the SIR polypeptide and the cytochrome c polypeptide. Since the specification fails to disclose the invention as claimed, it would require an extensive and undue amount of experimentation to practice the invention as claimed, especially in view of the fact that making transgenic organisms across the entire animal kingdom is considered highly unpredictable.

State Of Art And Predictability:

The state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Furthermore, allelic variations and the interactions between the allelic variants also influence a particular phenotype. These effects can dramatically alter the observed phenotype and therefore can influence or later the conclusions drawn form the transgenic or knockout models

Furthermore, the transgene expression and physiological consequences of transgene products in non-mouse mammals are not always accurately predicted among various species of mammals. The lack of understanding of essential genetic control elements make it difficult to predict the behavior of any transgene in any animal because the transgene expression is influenced by position effect in transgenic animals. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the expression of a transgene. The cis acting elements of one species may interact with different transactivating factors in other species. For example, the introduction of human growth hormone transgene in mice results in mammoth mouse phenotype, where as expression of the same transgene in pig results in premature death of transgenic pigs. Furthermore, many biochemical pathways are plastic in

nature, which reflects the ability of the embryo to use alternative gene when the preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, for example are the important factors that govern the expression of a transgene.

In addition, multicellular organisms are the current evolutionary summation of more than one billion years of selection. Their complexity means that even a humble mouse cannot be used as a simple tool. For example, extensive phenotype tests even in mice have shown that abnormal phenotypes were sometimes detected in physiological areas where they were not initially anticipated, or only manifested under certain conditions, emphasizing the need for careful phenotypic investigation. Nevertheless, the effect of some genes became evident only upon inactivation of another gene, pointing to the phenomenon of biological robustness. Therefore considering the scope of invention as claimed, at issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). The state of the transgenic art clearly concludes that poor embryo survival, low transgene integration rate and unpredictable transgene behavior are the three primary

contributors that determine that fate of a transgenic animal made. *see Taft et al Trends in Genetics 22(12):649-653, 2006; Linder, Lab. Anim. 30(5):34-39, 2001; Bilbo et al, Lab. Anim. 30(1):24-29, 2001; Holschneider et al, Int. J. Dev. Neuroscience 18 :615-618, 2000; Wood. Comp. Med. 50(1): 12-15, 2000; Sigmund, Arterioscler. Throm. Vasc. Biol. 20:1425-1429, 2000; Kappel et al. Current Opinion in Biotechnology 3:558-553 1992.*

In instant case making all possible transgenic organisms for the use in the claimed methods is not considered routine in the art and without sufficient guidance to a method to make a particular species the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Furthermore, the scope of the claims encompasses methods of testing a compound with any fragment of cytochrome c polypeptide having any function, as well as methods comprising the use of any proteins having deacetylase activity encoded by nucleic acids which hybridize under the conditions recited above to any fragments of a nucleic acid encoding the polypeptide of SEQ ID NO: 1, which is not commensurate with the disclosure of the specification.

In addition, claims 24-26 and 28-33 are drawn to the use of nucleic acids that hybridizes under 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C to the complement of a nucleic acid encoding an amino acid sequence of SEQ ID NO: 1. However, the scope of the claimed methods encompassing the use of any proteins encoded having deacetylase activity said nucleic acids, which include any proteins having 58% sequence identity to SEQ ID NO: 1, encoded by any polynucleotides having 86% sequence identity to the complement of polynucleotides that encode SEQ ID NO: 1, does not commensurate with the disclosure provided in the specification (see above 112 1st paragraph rejection under written description regarding the derivation of 86% sequence identity), because the specification does not provide adequate guidance with respect to making/isolating any proteins encoded by those nucleic acids having mutations/modifications in as many as 313-314 nucleotides, while retaining the specific enzymatic function, i.e., the deacetylase activity. The specification also lacks adequate guidance with regard to how the structural features nucleic acids correlate to function by providing a rational and/or predictable scheme for modifying as many as 313-314 nucleotides within those polynucleotides that encode SEQ ID NO: 1 with an expectation of obtaining the desired activity/function, i.e., deacetylase activity.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the invention as claimed is unpredictable and the experimentation left

to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

Claims 1-5, 8-11 and 22-33 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

This office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/JAE W LEE/
Examiner, Art Unit 1656

/Delia M. Ramirez/

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